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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	018743/0276324	1864

7590 07/25/2005

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/3/05, 2/10/05, 5/17/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 6-8, 10, 12-21, 23-25 and 28-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-8, 10, 12-21, 23-25 and 28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-4, 6-8, 10, 12-21, 23-25, 28, 29, and 31-40 are pending.

Applicant's traversal and the amendment to claims 1 and 12-14 in paper filed on 2/3/05 and the supplemental response summarizing the interview filed on 2/10/05 is acknowledged and considered. However, the amendment filed on 2/3/05 did not contain a marked-up copy of all of the amendments that were made to the amended claims. A non-responsive amendment was mailed to applicant on 4/28/05.

The amendment filed on 5/17/05 with the marked-up copy of amended claims is acknowledged and considered by the examiner.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/3/05 has been entered.

Election/Restrictions

The non-elected species in claims 16, 19, 32 and 37 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/15/01.

Claim Objections

Applicants are advised that should claim 30 be found allowable, claim 33 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The limitation "an increase in Factor IX is observed in said mammal," in claim 30 is inherent in claim 33 because delivering Factor IX by way of gene therapy to a mammal would result in an increase in Factor IX observed in the said mammal.

Applicant stated in the response filed on 2/3/05 that claim 30 has been cancelled without prejudice and the objection to claim 30 should be withdrawn.

Applicant's arguments filed 2/3/05 have been fully considered but they are not persuasive because claim 30 was cancelled in the amendment filed on 2/3/05 (which was not entered), however, the amendment filed on 5/17/05 has claim 30 pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 2, 4, 10, 24, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps for completing gene therapy, e.g., delivering of a nucleic acid encoding a coagulation protein to the mammal and expressing the coagulation factor in the mammal. Instant claims 3 and 6 provide the step(s) missing from the claim.

Claims 2, 4, 10, 24, and 28 are rejected because they depend on claim 1 and do not recite the missing method step(s).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The claimed methods read on either preventing or inhibiting the formation of inhibitory antibodies to a protein (blood coagulation protein) delivering to a mammal by way of gene therapy, wherein said mammal has a genetic defect which can result in generation of inhibitory antibodies against a protein (blood coagulation protein), said method comprising administering cyclophosphoamide prior to or simultaneously with a nucleic acid encoding the protein, wherein the protein is the same species as said mammal. The claimed methods also read on a method of gene therapy comprising delivering a nucleic acid encoding a coagulation factor and an immunosuppressive agent to a mammal, wherein the mammal has a genetic defect that might result in generating inhibitory antibodies (e.g., the mammal does not express the coagulation protein because the gene encoding the protein is mutated resulting in no expression of the protein).

Claims 1, 2, 3, 4, 6, 10, 12, 13, 14, 15, 16, 19, 20, 28, 29, 30, 31, 32, 33, 35, 37, 38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) in further view of Tripathy et al., (Nat. Med. 1996, 2:545-550).

Wilson teaches a gene therapy method comprising co-administering with a viral vector an immunosuppressive agent to a human (column 2, lines 35-52, column 4, lines 20-34 and column 25-26). The method is directed to reducing the immune response to foreign proteins by coadminstering the immunosuppressive agent with the viral vector. Wilson teaches that an

immune response can be the product of the transgene when that transgene expresses a protein that is foreign to the treated host (column 1, lines 63-65). Wilson cites prior art that teaches that tolerlization to Factor IX and vector antigens allows for long-term expression (page 3). Wilson teaches co-administering cyclophosphamide with the viral vector (column 5, line 52-column 6, line 23 and column 8, lines 34-45). Wilson teaches that the immunosuppressive agent may be administered prior to or concurrently with the recombinant viral vector (column 2, lines 45-49). However, Wilson does not specifically teach using a nucleotide sequence that is the same species as said mammal. In addition, Wilson does not specifically teach using a mammal having a genetic defect, which can result in generation of inhibitory antibodies to a blood coagulation factor in the method.

However, at the time the invention was made, Bach teaches an in vivo or an ex vivo method of combining an immunosuppressive agent and at least one virus comprising a DNA containing a therapeutic gene (see abstract and page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Bach teaches that the invention makes it possible to achieve therapeutic effect, which is markedly prolonged (page 2 of the US 2003/0004091, which is the English equivalent of WO 96/25177). The DNA or therapeutic gene is from human, which would read on an in vivo method delivering a human therapeutic gene to a human since a human lacking a protein would require a protein with similar biological activity (page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Bach teaches that the therapeutic gene can encode factors VII, VIII, and IX (page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Using the therapeutic gene encoding Factors VIII or

IX in the method would require a mammal with hemophilia (a genetic defect, which can result in generation of inhibitory antibodies to the protein. See page 5 of the instant specification).

In addition, at the time the invention was made, Tripathy teaches that novel proteins delivered by way of gene therapy, including deficient human proteins in patients with recessive diseases generate immune responses (page 549).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach in further view of Tripathy to co-administer cyclophosphamide with a recombinant virus to a mammal, wherein the virus comprises a nucleotide sequence encoding a blood coagulation protein, e.g., Factor IX, wherein the protein is from the same species as said mammal. One of ordinary skill in the art would have been motivated to co-administer an immunosuppressive regimen with gene therapy, wherein the delivered protein being the same species as said mammal because the art of record teaches that exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein. In addition, one of ordinary skill in the art would have been motivated, as a matter of designer's choice, to deliver a nucleic acid encoding a protein being the same species as the mammal because a protein with similar biological activity would be required to replace the lack of expression from the protein. Furthermore, the method taught by Wilson taken with Bach in further view of Tripathy has the same limitations as required by the claimed method because the method taught by Wilson taken with Bach in further view of Tripathy uses the same material(s) and method(s). Therefore, the method taught by Wilson, Bach and Tripathy would reduce the immune response to the foreign protein and viral vector antigens since both are presented by MHC class I molecules.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach in further view of Tripathy to co-administer cyclophosphamide with a recombinant viral vector to a mammal, wherein the mammal has a genetic defect which can result in generation of inhibitory antibodies to a blood coagulation protein. One of ordinary skill in the art would have been motivated to co-administer an immunosuppressive regimen (cyclophosphamide) with gene therapy to the mammal to improve the expression of the coagulation protein (Factor VIII or Factor IX) by preventing or inhibiting the formation of inhibitory antibodies to the blood coagulation protein and viral vector antigens.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/3/05 have been fully considered but they are not persuasive because.

In response to applicant's argument that Herzog (Blood 90 part 1, Supp. 1 abstract 1057, 1997) teaches away from the claimed method, the argument is not found persuasive because one of ordinary skill in the art understands that intramuscular injection of AAV results in transduction of muscle fibers without activating destructive T cell responses even with transgenes that encode foreign proteins (Chirmule et al. Gene Therapy, 6, pages 1574-1583, 1999 and Xiao et al. Molecular Therapy, 1, pages 323-329, 2000 and US 2003/0130221). Furthermore, the claims are not limited to only intramuscular injection of AAV encoding canine FIX to hemophilia dogs.

In response to applicant's argument that the amended claims require that the mammal or human has a genetic defect which can result in generation of inhibitory antibodies to a protein or blood coagulation protein, the argument is not found persuasive because the limitation does not require the mammal to produce inhibitory antibodies. The mammal just has to have a genetic defect that can result in inhibitory antibodies (e.g., hemophilia).

In response to applicant's argument that Wilson and Bach do not specifically teach a method of preventing the formation of inhibitory antibodies in a gene therapy method, the argument has already been address in several previous office actions and is not found persuasive for the reasons of record. See the response to applicant's argument set forth in office actions mailed on 7/29/04 and 1/9/04. Furthermore, Wilson teaches that "CTLs are thus an important effector in the destruction of target cells, with activation occurring in some cases in the context of the transgene product, or of the viral-synthesized proteins, both of which are presented by MHC class I molecules (column 1)." Thus, even if Wilson is directed to reducing the immune response to the viral vector, the method taught by Wilson would also reduce the immune response to the foreign protein since both proteins are presented by MHC class I molecules.

In response to applicant's argument that one of ordinary skill in the art would not use an immunosuppressive agent with a gene therapy because Tripathy report studies of gene therapy where mice injected with adenovirus harboring murine EPO did not develop anti-EPO antibodies, the argument is not found persuasive because the mice used in the Tripathy study did not have a genetic defect which can result in generation of inhibitory antibodies.

Claims 1, 12, 13, 14, 21, 23, 24, 25, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) and Tripathy et al., (Nat. Med. 1996, 2:545-550) as applied to claims 1-4, 6, 10, 12-16, 19, 20, 28-33, 35, 37, 38 and 40 above, and further in view of Nilsson (PNAS, 83:9169-9173, 1986) and Warrier (Blood Coagul Fibrinolysis, 1998; 9 Suppl 1: S125-8).

The rejection of the base claims 1, 12, 13, and 14 under 35 U.S.C. 103(a) is applied here as indicated above, by Wilson taken with Bach in further view of Tripathy. However, Wilson, Bach and Tripathy do not specifically teach using a mammal that has no detectable endogenous expression of the blood coagulation protein or said mammal that has hemophilia B and inhibitory antibodies that bind specifically with Factor IX (FIX) protein.

However, at the time the invention was made, Nilsson teaches a complication of Factor IX therapy is the development of antibodies to Factor IX (page 9169). Furthermore, Warrier teaches that the development of inhibitory antibodies is a serious complication of hemophilia B (pages S125-8). Inhibitors are commonly associated with the total absence of FIX antigen due to total deletions or other major derangements of the FIX gene (pages S125-8). Thus, in view of the art of record, inhibitory antibodies to Factor IX protein in a mammal having hemophilia B are the result of the mammal not expressing the Factor IX protein.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach and Tripathy in further view of Nilsson and Warrier to co-administer an immunosuppressive agent with a viral vector comprising a nucleotide sequence encoding a Factor IX protein to a mammal that has no detectable endogenous expression of the FIX protein. One of ordinary skill in the art would have

been motivated to combine the teaching and use the method of Wilson, Bach and Tripathy in a mammal that has no detectable endogenous expression of the FIX protein because the art of record teaches that the major problem with Factor IX therapy is the development of antibodies to Factor IX. Thus, one of ordinary skill in the art would reasonably conclude that using the method taught by Wilson, Bach and Tripathy would inhibit or prevent the development of inhibitory antibodies to FIX protein because the method uses the same material and methods steps as required in the instant claimed method.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach and Tripathy in further view of Nilsson and Warrier to co-administer an immunosuppressive agent with a viral vector comprising a nucleotide sequence encoding a FIX protein to a mammal that has hemophilia B and inhibitory antibodies that bind specifically with FIX protein. One of ordinary skill in the art would have been motivated to combine the teaching and use the method taught by Wilson, Bach and Tripathy in a mammal having hemophilia B and having inhibitory antibodies that bind specifically with FIX protein because the mammal having hemophilia B requires FIX therapy and the art of record teaches that inhibitory antibodies would develop in the mammal because the development of inhibitory antibodies to FIX protein is a complication of hemophilia B. Thus, one of ordinary skill in the art would reasonably conclude that using the method taught by Wilson, Bach and Tripathy would inhibit or prevent the development of inhibitory antibodies to FIX protein because the method uses the same material and methods steps as required in the instant claimed method.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/3/05 have been fully considered but they are not persuasive because of the same reasons as set forth above in the prior response to applicant's argument against the previous 103(a) rejection.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The argument against Warrier or Nilsson not teaching the claimed method has already been addressed in the previous office action mailed on 7/29/04.

In response to applicant's argument that Nilsson teaches away from using the cyclophosphamide with gene therapy because Nilsson states that cyclophosphamide combined with Factor IX treatment was ineffective (page 9173), the argument is not found persuasive because Nilsson was only cited in the 103(a) rejection to display that Factor IX therapy in hemophiliacs produce antibodies against Factor IX.

Claims 1, 3, 6, 7, 8, 13, 14, 16, 17, 18, 33-36, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) and Tripathy et al., (Nat. Med. 1996, 2:545-550) as applied to claims 1-4, 6, 10, 12-16, 19, 20, 28-33, 35, 37, 38 and 40 above, and further in view of Herzog et al., (IDS, PNAS, vol. 94, pages 5804-5809, 1997).

The rejection of the base claims 1, 3, 6, 13, 14, 16, 33, 35, and 40 under 35 U.S.C. 103(a) is applied here as indicated above, by Wilson taken with Bach in further view of Tripathy. However, Wilson, Bach and Tripathy do not specifically teach using a recombinant adeno-associated viral vector (rAAV) in the method.

However, at the time the invention was made, Herzog teaches that AAV viral vectors can be used to deliver therapeutic levels of FIX after injection and can be used for treating patients with hemophilia B (page 5804).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson and Bach and Tripathy in further view of Herzog to use rAAV in the methods. One of ordinary skill in the art would have been motivated to use rAAV in the methods because Herzog teaches that AAV viral vectors can be used to deliver therapeutic levels of FIX after intramuscular injection and can be used for treating patients with hemophilia B.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/3/05 have been fully considered but they are not persuasive because of the same reasons as set forth above in the prior response to applicant's argument against the primary 103(a) rejection.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here because

Herzog was only cited in the rejection to show that AAV can be used in the claimed method. The method was already taught in the primary 103(a) rejection. In response to applicant's argument that one of ordinary skill in the art would not use an immunosuppressive agent with a gene therapy because Herzog report studies of gene therapy where mice injected with AAV encoding FIX did not develop inhibitory antibodies, the argument is not found persuasive because the mice used in the Herzog study did not have a genetic defect which can result in generation of inhibitory antibodies. Unlike a mammal with a genetic defect that results in inhibitory antibodies to FIX, the mice in Herzog have circulating Factor IX.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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